TORSADE DE POINTES AND SUDDEN DEATH ASSOCIATED WITH DIABETIC AUTONOMIC DIARRHOEA - A CASE REPORT

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ABSTRACT

A 68-year-old diabetic and hypertensive woman presented with chronic autonomic diarrhoea, syncope and palpitations which were associated with QT prolongation and recurrent episodes of torsade de pointes. She was on glibenclamide, indapamide and probucol (for type V hyperlipidaemia). Despite intravenous infusions of potassium, lignocaine and amiodarone, the unstable rhythm persisted. However, intravenous magnesium sulphate with small doses of intravenous propranolol terminated the torsade de pointes.

She was stabilised but following discharge she relapsed, and upon re-admission, succumbed to intractable ventricular fibrillation. Early recognition and aggressive treatment of this condition is emphasised. Multiple aggravating factors ie autonomic diarrhoea resulting in severe potassium and magnesium depletion, kaliuretic effect of indapamide, probable QT prolongation associated with diabetic autonomic neuropathy and probucol; probable underlying coronary artery disease and heightened emotional and sympathetic discharge could have contributed to this very unstable ventricular arrhythmia and sudden death.

Keywords: *diabetic autonomic neuropathy, diarrhoea, hypokalaemia, hypomagnesaemia, indapamide, torsade de pointes*

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INTRODUCTION

Autonomic dysfunction occurs in long-standing diabetic patients and contributes to cardiovascular morbidity in several ways, including inappropriate cardiovascular responses to stress, postural changes, respiration, Valsalva manoeuvres, painless myocardial ischaemia, and non-coronary myocardial dysfunction[1]. Recently, QT prolongation has been reported[2-4]. The significance of the latter remains unknown, although increased risk for sudden arrhythmic death has been suggested[4,5].

We report an unusual case of an elderly diabetic woman who presented with chronic diarrhoea, palpitations and syncopal attacks associated with grossly prolonged QT interval and torsade de pointes. The multifactorial synergism contributing to this fascinating syndrome is emphasised.

CASE REPORT

A 68-year-old Chinese woman was referred for further management of an intractable ventricular tachyarrhythmia by a private physician. This long-standing diabetic (type II, non-insulin dependent) and hypertensive woman presented with palpitations, near-syncopal and syncopal attacks for the past 2 days when she was admitted to a private hospital.

Electrocardiographic (ECG) monitoring at this first admission showed salvos of polymorphous ventricular tachycardia associated with marked QTU prolongation (corrected QTU interval 0.65 second, see Fig 1). She was found to have severe hypokalaemia (serum potassium 2.1 mmol/l) for which intravenous potassium, lignocaine boli (50-100 mg) and infusions (from 2-4 mg/min), and amiodarone (300 mg stat, then 50mg/h) were given. However, the arrhythmia recurred with the patient lapsing in and out of consciousness associated with longer runs of the polymorphous ventricular tachycardia. However, light praecordial thumps transiently reverted the arrhythmia. She was then transferred to our hospital for further management.

On admission to our coronary care unit, she appeared somewhat obtunded, had recurrent lapses of conscious levels, with a variable heart rate of 80 to 150 beats/min, and supine blood pressure 110/75 mmHg. The apical impulse was not felt, the heart sounds were dual with no added sounds, her lungs were clear, the abdomen obese, soft with no visceral enlargement or mass, and the bowel sounds were well-heard. She had diminished peripheral reflexes and glove-stocking hypoaesthesiae, but no lateralising signs.

The monitored ECG rhythm was recognised as torsade de pointes, associated with grossly prolonged QTU interval (QTc 0.67 s) with large T-U waves, some with notching (see Fig 2). Some degree of pause-dependency involving arrhythmia initiation was noted, with post-pause enlarged U waves being quite evident. No recent hyperacute myocardial ischaemic or infarct patterns were noted. Arterial blood gas showed respiratory-compensated mild metabolic acidosis (pH 7.42, pO_2 11.6 mmol/l, O_2-saturation 97%, pCO_2 3.52 mmol/l, HCO_3 17.5 mmol/l, base deficit - 4.6 mmol/l), and severe hypokalaemia (1.9 mmol/l). Intravenous potassium was infused (up to 20 mmol/hour), lignocaine boli (75-100 mg) were instituted followed by 4 mg/min infusion and amiodarone infusion was stopped. However, the torsade phenomena persisted with episodes of impaired consciousness, reverting with light praecordial thumps. Intravenous magnesium sulphate (20% solution in normal saline) was begun at 50 mg/min. Whilst the patient was being prepared for overdrive pacing, further intravenous boli of 0.5 mg (x2) propranolol was given. Within 10 minutes, torsade de pointes episodes reverted to sinus rhythm!

A repeat 12-lead ECG showed no new infarct or ischaemic pattern, and the corrected QT interval remained prolonged (0.53 s), with prominent U-waves. She was stabilised on oral propranolol 80 mg q.i.d., soluble insulin s.c. t.i.d., and intravenous potassium and magnesium supplements were continued. Investigations showed: blood glucose 21.8 mmol/l (corrected

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Fig 1 - 12-lead ECG taken 2 days prior to the first hospitalisation. Note that the resting heart rate was 86 beats per minute, the mean QTU interval was 0.54 s (QTc 0.65 s, by Bazett's formula). Note also that the T waves merge into the large U waves, some with barely discernible notching - eg in leads 2, 3, V1-V3. Some degree of intraventricular block is also evident - QRS interval about 0.10 s with loss of septal activation waves. Her serum potassium was measured at 2.1 mmol/l.

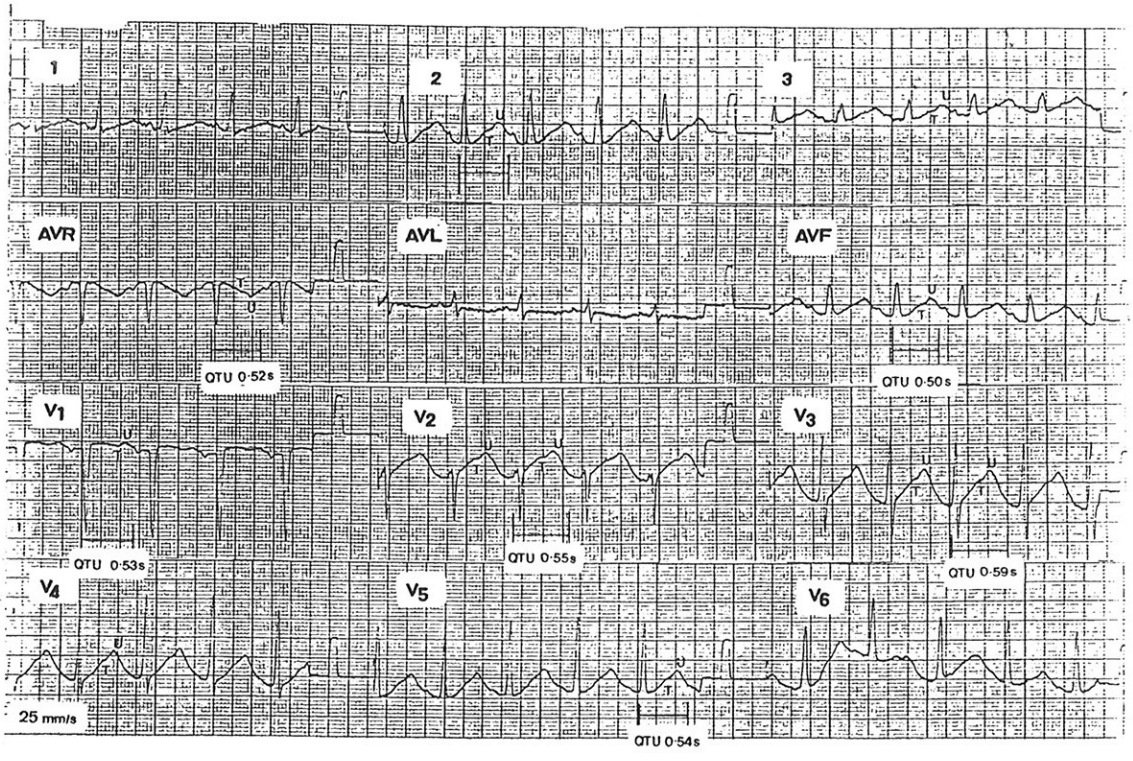
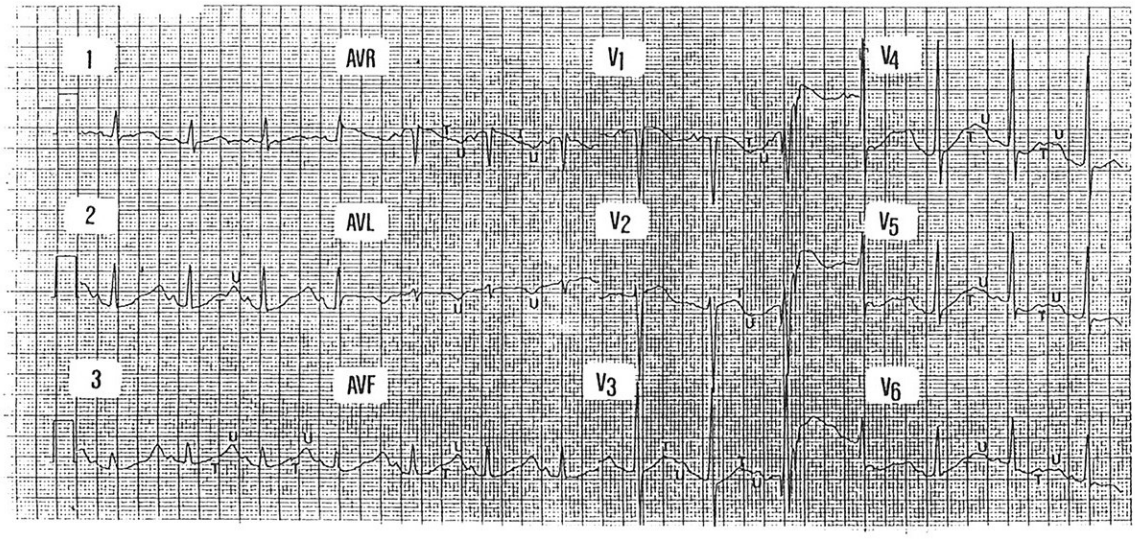


Fig 2A - 12-lead ECG taken upon transfer to the coronary care unit of the second hospital. The heart rate was 80 beats per minute, QTU interval 0.58 s (QTc 0.67 s). Similarly the T waves and the enlarged U waves merge together with almost imperceptible notching.



within the day to 9.8 mmol/l); haemoglobin 11.2 mg/dl, white cell count 10.4 x 10^9/ul (polymorphs 80%), serum sodium 124 mmol/l, potassium 2.3 mmol/l, urea 4.0 mmol/l, creatinine 92 umol/l, albumin 37 g/l, globulin 25 g/l, calcium 1.78 mmol/l, phosphate 1.17 mmol/l, alkaline phosphatase 57 i.u., alanine transaminase 92 i.u., aspartate transaminase 285 i.u. (down to 46 i.u. by the second day); creatine kinase 899 i.u. (down to 309 i.u. by day 2, CK-MB fraction absent); lactate dehydrogenase 1249 i.u. (833 i.u. by day 2, LD2 and LD5 isoenzymes > LD1); magnesium 0.48 mmol/l (persistently low: 0.50, 0.53 mmol/l even at day 2); plasma osmolality 308 mOsm/kg, urine osmolality 479 mOsm/kg; admission spot urine biochemistry: pH 5.5, sodium 129 mmol/l, potassium 46.3 mmol/l, chloride 163 mmol/l; 24-hour urinary electrolytes: urine volume 2.45 litres, sodium 245 mmol (normal 40-220), potassium 59 mmol (normal 26-123), chloride 262 mmol (110-250). Thus her urine biochemistry confirmed excessive and inappropriate renal potassium and sodium loss, but normal

Fig 2B - Continuous ECG strip showing variable runs of torsade de pointes (rate 160-330 per minute, classical twisting characteristic about the isoelectric axis). The small arrows and symbol 'U' show the abnormally enlarged post-pause 'arrhythmogenic U waves' - these are thought to be the early afterdepolarisations responsible for triggered firing of the torsade phenomena.[15] The serum potassium and magnesium were 1.9 and 0.48 mmol/l respectively.

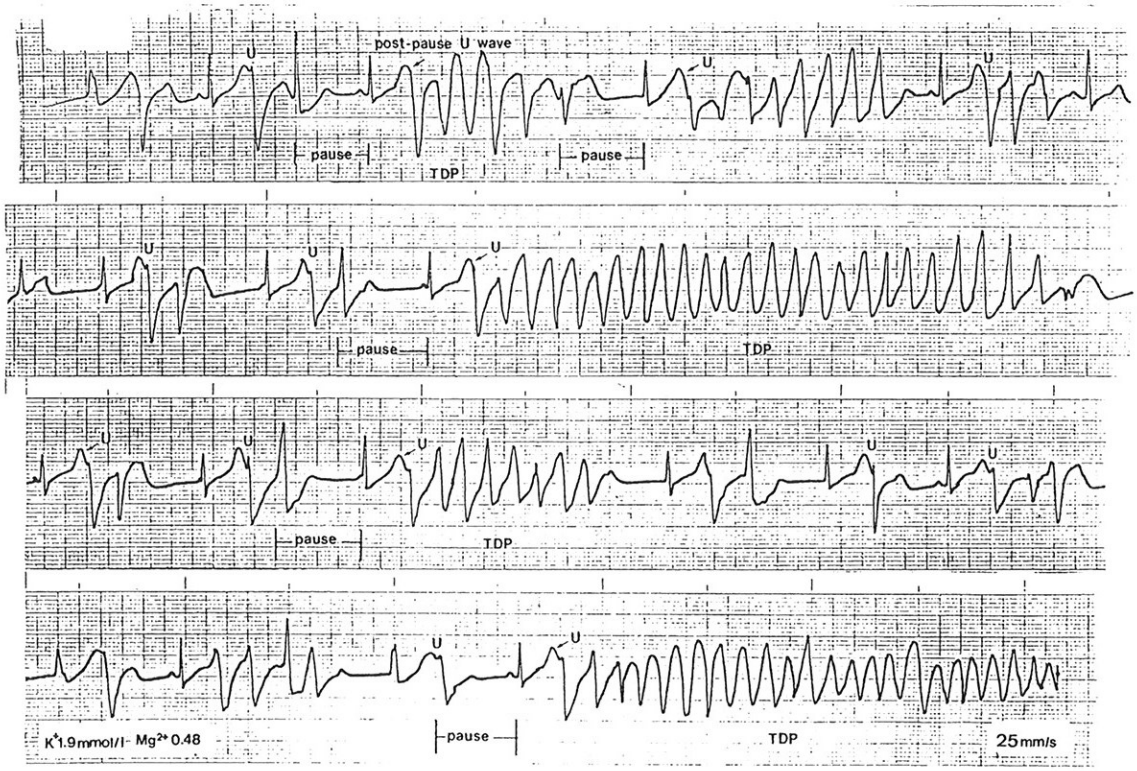
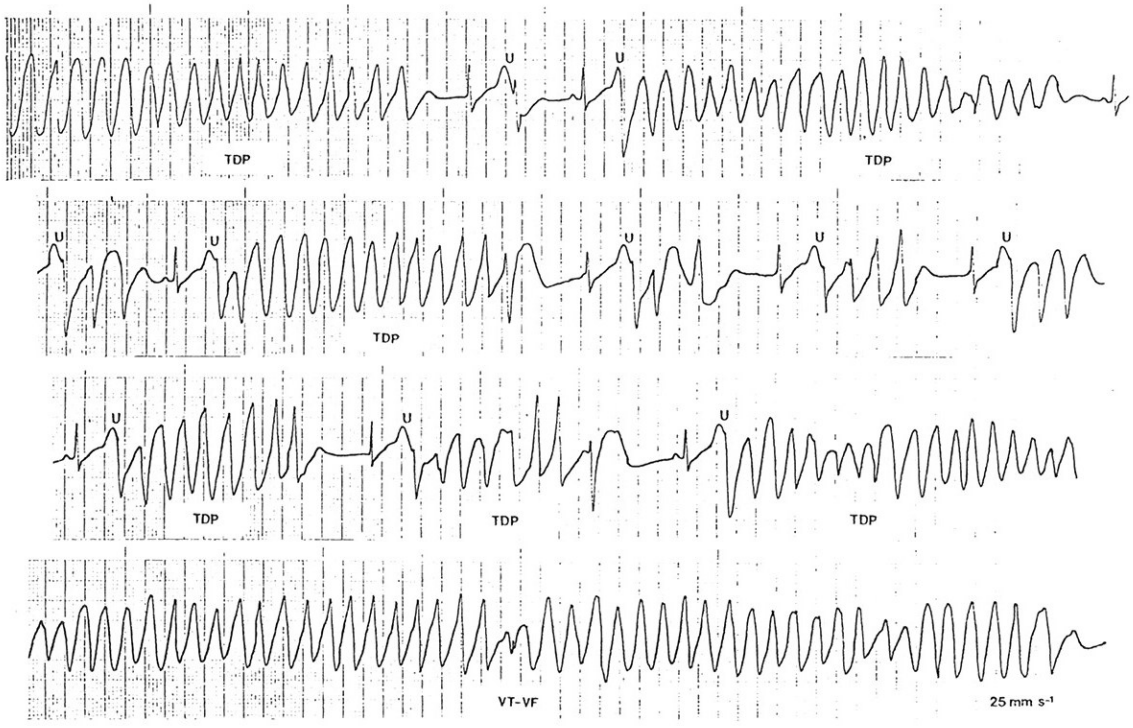


Fig 3 - Pre-terminal ECG: Continuous recording showing repetitive runs of torsade de pointes (TDP) - variable paroxysms of which terminated spontaneously. The late cycle phases of the very prominent post-pause U waves appeared to be the foci of origin of the torsade de pointes. The rate for the TDP varied from 240 to 280 beats per minute. The QTU (uncorrected) interval averaged 0.45 second. (Note that there seemed to be a correlation between the length of the post-pause duration and the accentuation of the U waves.) The final prolonged salvo of TDP deteriorated into a ventricular tachycardia-fibrillation (VT-VF).



acidification and concentration.

During the next 2 days she passed loose, watery stools 8 to 12 times a day! A review of her past medical and drug history was obtained from both her physician and family. This lady had chronic diabetes for 20 years, and was treated with variable sulphonylureas, latterly glibenclamide 5 mg daily. She also had type V hyperlipidaemia (grossly turbid serum, serum triglycerides 8 - 15 mmol/l, total cholesterol 6.5 - 7.5 mmol/l, HDL-cholesterol 0.5-1.2 mmol/l) for which she was earlier treated with dietary advice, cholestyramine, bezafibrate, gemifibrozil. For the last one year or so she was given only probucol. She had been on indapamide 2.5 mg daily for the past 2-3 years for mild hypertension. Over the past 18 months, she admitted to progressively more frequent passage of loose to watery stools, the last week of which was quite troublesome ie about 6-10 times daily. Just prior to admission she was quite wheelchair-bound because of increasing lower limb fatigue and cramps, as well as postural hypotension. A clinical diagnosis of autonomic diarrhoea was made and she was given doxycycline 200 mg per day, and by the third day she had formed stools only twice that day.

She recovered with normalisation of her electrolytes (except serum magnesium, which remained low - 0.58 mmol/l), and remained in sinus rhythm with near-normalisation of the QTc interval (0.47s). Her stools grew only 'normal flora' with no occult blood. She had moderately severe postural hypotension, but was otherwise unable to cooperate fully with other autonomic tests[6]. She was discharged against medical advice by day 7, with oral propranolol 40 mg t.i.d., glibenclamide 2.5 mg daily, potassium chloride 2 g t.i.d. and magnesium chloride 10 ml (10 mmol) q.i.d., and doxycycline 200 mg daily for another 2 weeks. Probucol and indapamide were stopped, and dietary prudence was emphasised. We were unable to analyse her blood for levels of probucol or indapamide.

However, 2 days later, she was readmitted for similar episodes of palpitations and near-syncope. Apparently she had some domestic arguments with family members, and refused medications and food. On admission, she was highly stressed and confused. Her pre-terminal blood electrolytes showed serum potassium 3.8 mmol/l, serum magnesium 0.57 mmol/l. Her rest electrocardiogram however, showed a sinus tachycardia of about 100 beats per minute, interspersed with frequent runs of torsade de pointes (see Fig 3). The QT interval was measured at an average of 0.45 second (QTc 0.58 s). There was no evidence of recent myocardial infarction. Her cardiac rhythm deteriorated rapidly into intractable and terminal ventricular fibrillation and she died despite prolonged cardiopulmonary resuscitation.

DISCUSSION

This patient presented with an unusual interplay of metabolic and cardiovascular abnormalities almost all of which may be attributed to her long-standing diabetes and its complications. She had chronic diabetic autonomic diarrhoea with autonomic dysfunction ie postural hypotension and peripheral neuropathy. Her loose and frequent bowel movements worsening over the last 18 months with normal cultures of gut flora, and the rapid improvement with gut antibiotics (ie doxycycline) lend support to the idea that bacterial overgrowth over segments of autonomic-denervated gut was the source of her diarrhoea. Large and frequent stool movements had contributed to her intestinal loss of both potassium and magnesium.

Although indapamide is a mild diuretic hypotensive agent, some degree of kaliuresis is known to occur[7]. While mild urinary potassium loss in most treated people is asymptomatic, in this instance, further hypokalaemia might have aggravated the already unstable state of this patient. We detected some inappropriate urinary potassium and sodium loss in this patient, although we could not altogether exclude some renal tubular disorder here.

What about probucol? This agent has been shown to be associated with prolongation of the QT interval - although the clinical significance is not fully established[8-10]. Thus, can this agent given over the last period of her treatment be another factor contributing to her unusual arrhythmia? This cannot be ruled out. Matsuhashi et al had reported torsade occurring in a patient with probucol-induced prolonged QT interval[11]. Recently, diabetic autonomic neuropathy has been shown to prolong electrocardiographic QT interval when compared to control groups[2-5]. It has been suggested that differential denervation of the sympathetic and parasympathetic nerves supplying the heart is the cause[5]. However, torsade de pointes ventricular tachycardia has not been documented in this context.

It appears that the grossly abnormal hypokalaemia and hypomagnesaemia might be the major factors contributing to the QT prolongation in this patient[12]. But, even prolonged QT intervals per se may not be accompanied by torsade de pointes, although most pre-torsade QTc intervals exceed 0.56 to 0.60 second[13]. Triggered firing has been thought to be the initiating mechanism of this arrhythmia. For example, pause-dependent torsade occurs in close relationship to the post-pause 'arrhythmogenic U waves' which are considered the early afterdepolarisation waves responsible for triggered firing of the arrhythmia[14,15]. The exact mechanism(s) for torsade de pointes remains speculative, but has been extensively reviewed[16-19]. Whilst some authorities believe that asynchronous repolarisation in the face of increased dispersion of refractoriness of the myocardium or conducting pathways is involved in the activation wavefront of this arrhythmia, others increasingly believe that such 'delayed repolarisation phenomena' may be viewed as 'afterdepolarisations' whether early or late[15]. We believe that all these multiple factors act in concert to propagate this unstable rhythm - torsade de pointes is an arrhythmia of 'maximal vulnerability"[20].

The management of this patient was clearly difficult. We were lulled into a sense of complacency when we could recognise and revert the unstable rhythm so convincingly. We noted that she was still somewhat depleted of total body magnesium when she was discharged, although her potassium normalised. Her ECG had shown residual QT prolongation suggesting perhaps that her vulnerable state still remained, ie as a manifestation of diabetic autonomic dysfunction. It is generally agreed that hypomagnaesemia is difficult to treat. Prolonged intravenous magnesium remains the best option, but is often impractical. The gut absorption of oral magnesium is poor and may cause osmotic diarrhoea; nevertheless, we elected to cautiously offer this mode of therapy. The efficacy of such oral therapy is not established, although an anecdotal report from Prof R W F Campbell (personal communication) suggested that in one such patient, recurrent ventricular tachycardia was prevented by oral magnesium supplements.

The recommended treatment of torsade de pointes has been extensively reviewed[21]. Immediate management of torsade de pointes implies quick recognition of this arrhythmia, and its underlying causes. Importantly metabolic and electrolyte abnormalities must be rapidly corrected. Drugs known to cause QT prolongation or torsade (eg probucol in this patient) should be identified and discontinued. It is now quite well-established that Class IA antiarrhythmic agents have no place in its treatment, as they may worsen the QT prolongation[15,21]. Lignocaine, beta-blockers, isoprenaline and phenytoin can be used.

Continuous electrocardiographic monitoring is mandatory; preferably till all the contributing factors have been corrected, QT/QTc intervals normalised, or when no further episodes of

torsade recur for 48 hours. Here we found intravenous magnesium sulphate and propranolol useful. In recent reports, magnesium infusion was successful in rapid suppression of the torsade phenomena in the majority, often within 30 minutes[22,23]. We added propranolol because we felt there was some adrenergic stimulation in this patient. For beta-blockade, the maximal-tolerated dose is that usually recommended. Overdrive pacing remains the optimal method of therapy, and this should not be delayed. Electroshock cardioversion is useful as a temporary measure, although relapses are common. Finally all the contributing factors should be identified and, where possible, treated.

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REFERENCES

1. Ewing JK, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. Q J Med 1980;49:95-108.
2. Page M, Watkins PJ. Cardiorespiratory arrest and diabetic neuropathy. Lancet 1978;i:14-6.
3. Pont A, Rushing JL, Kelsey T, Jacobs L. Cardiorespiratory arrest and diabetic autonomic neuropathy. Lancet 1978;i:386-7.
4. Kahn JK, Sisson JC, Vinik AI. QT interval prolongation and sudden cardiac death in diabetic autonomic neuropathy. J Clin Endocrinol Metab 1987;64:751-4.
5. Bellavere F, Ferri M, Guarini L, Bax G, Piccoli A, Cardone C, et al. Prolonged QT period in diabetic autonomic neuropathy: a possible role in sudden cardiac death? Br Heart J 1988;59:379-83.
6. Quek DKL, Khor PG, Ong SBL, Chan PYM, Khalid BAK. Assessment of cardiovascular autonomic dysfunction in diabetic patients: which tests to perform? J ASEAN Fed Endocrinol Soc 1987;6:58-71.
7. Leonetti G, Rapelli A, Salvetti A, Scapellato L. Long-term effects of indapamide: final results of a 2-year Italian multicenter study in systemic hypertension. Am J Cardiol 1990;65:67H-71H.
8. Klein L. QT-interval prolongation by probucol. Arch Intern Med 1981;141:1102-3.
9. Troendale G, Gueriguian J, Sobel S, Johnson M. Probucol and the QT interval (letter). Lancet 1982;i(8282):1179.
10. McCaughan D. Probucol and the QT interval (letter). Lancet 1982;ii(8290):161.
11. Matsuhashi H, Onodera S, Kawamura Y, Hasebe N, Kohmura C, Yamashita H, et al. Probucol-induced QT prolongation and torsade de pointes. Jpn J Med 1989;28(5):612-5.
12. Keller PK, Aronson RS. The role of magnesium in cardiac arrhythmias. Progr Cardiovasc Dis 1990;32:433-48.
13. Stern S, Keren A, Tzivoni D. Torsade de pointes: definitions, causative factors, and therapy: Experience with 16 patients. Ann NY Acad Sci 1984;427:234-40.
14. Jackman WM, Clark M, Friday KJ, et al: Ventricular tachyarrhythmias in the long QT syndromes. Med Clin North Am 1984;68:1079-109.
15. Jackman WM, Friday KJ, Anderson JL, Aliot EM, Clark M, Lazzara R. The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. Progr Cardiovasc Dis 1988;31:115-72.
16. Coumel P, Leclercq JF, Lucet V. Possible mechanisms of the arrhythmias in the long QT syndrome. Eur Heart J 1985 (suppl);104:194-8.
17. Schwartz PJ, Periti M, Malliani A. The long QT syndrome. Am Heart J 1975;84:378-90.
18. Schwartz PJ: Idiopathic long QT syndrome: progress and questions. Am Heart J 1985;109:399-411.
19. Surawicz B, Knoebel SB. Long QT: good, bad or indifferent? J Am Coll Cardiol 1984;4:398-413.
20. Wiggers CJ. The mechanism and nature of ventricular fibrillation. Am Heart J 1940;20:399-412.
21. Stratmann HG, Kennedy HL. Torsades de pointes associated with drugs and toxins: recognition and management. Am Heart J 1987;113:1470-82.
22. Tzivoni D, Karen A, Cohen AM, Loebel H, Zahavi I, Chenzbraun A. et. al. Magnesium therapy for torsade de pointes. Am J Cardiol 1984;53:528-30.
23. Perticone F, Adinolfi L, Bonaduce D. Efficacy of magnesium sulfate in the treatment of torsade de pointes. Am Heart J 1986;112:847-9.